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Breast Conserving Surgery and Whole Breast Radiation therapy Followed by High Dose Rate Brachytherapy Boost Versus Electron Beam Boost in the Treatment of Early Breast Cancer in Young Indian Women: Which is Cosmetically Better?

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Background- Breast conserving treatment (BCT) is the treatment of choice in early breast cancer. Despite years of observation it is still regarded as controversial – not in regard to the very idea; the controversy pertains rather to the way it is being performed by radiation oncologists and surgeons. There are no uniform indic-ations as far as the optimal surgery range is concerned (lumpectomy alone, lumpectomy with the macroscopic margin of 1cm, excision of the breast tissue block of a segment or a quadrant). BCT has produced survival equivalent to mastectomy in the treatment of patients with early-stage invasive breast carcinoma in several randomized Phase III clinical trials.

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Strictly as per the compliance and regulations of:

Breast Conserving Surgery and Whole Breast Radiation therapy Followed by High Dose Rate Brachytherapy Boost Versus Electron Beam Boost in the Treatment of Early Breast Cancer in Young Indian Women: Which is Cosmetically Better?

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I. Background

Breast conserving treatment (BCT) is the treatment of choice in early breast cancer. Despite years of observation it is still regarded as controversial – not in regard to the very idea; the controversy pertains rather to the way it is being performed by radiation oncologists and surgeons. There are no uniform indic-ations as far as the optimal surgery range is concerned (lumpectomy alone, lumpectomy with the macroscopic margin of 1cm, excision of the breast tissue block of a segment or a quadrant). BCT has produced survival equivalent to mastectomy in the treatment of patients with early-stage invasive breast carcinoma in several randomized Phase III clinical trials.

Breast irradiation is an essential element of the conservative approach. Local recurrence risk after surg-ery alone reaches 35%, compared to 10% in patie-nts undergoing adjuvant radiotherapy [1]. First, the who-le breast is irradiated using external beam technique, us-ally with a dose of 50Gy. Subsequently it is nec-essary to increase the dose delivered to the tumour bed using a so called "boost".

Primary boost dose methods include telera-diotherapy (TRT) with external photon or electron beam (usually) and high dose rate (HDR) or low dose rate (LDR) brachytherapy (BT) [2]. The cost and time requ-ired (for both the patient and physician) for these two boosting techniques differ greatly. Whole-breast EBRT Inv-olves a 6-week course of fractionated treatments.

In contrast, BT can be completed in a 4- to 5-day tr-eatm-ent course. In addition, BT adds the risk of an in-vasive procedure with an outcome that is highly dep-en-dent upon the expertise of the physician/physicist tea-m.Biomathematical models are often used to estimate equivalent high-dose-rate regimens. For exam-ple, linear quadratic modelling has suggested that a hi-gh-dose-rate regimen of 5 fractions of 310 cGy per fraction should approximate the early and late effects of a 20-Gy low dose rate delivered at 0.5 Gy/h. Although biomathematical models can be used to estimate the appropriate dose, there is no standardized high-dose-rate fractionation schedule that can be recommended [3,4,5].

In two studies the efficacy of HDR BT and TRT as a boost in non-advanced breast cancer patients with breast conserving treatment was compared. First, whole breast irradiation was performed using an external photon beam (50Gy in classical fractionation). Subse-quently Hammer et al. delivered a boost to the tumour bed using either an electron beam (TRT-11Gy in 5 fractions) or HDR BT (single 10Gy boost). Local recurence rates were 8.2% and 4.3% ($p<0.04$), respe-ctively. Excellent or good cosmetic results were achiev-ed in 70% and 88%, respectively ($p<0.0001$) [6].

Polgar et al., in a randomized clinical Phase III trial, after the first stage of the study randomized the patients into 2 groups. In the first group the patients received external electron beam therapy of 16Gy in 8 fractions. In the second group the same total dose was delivered in the form of HDR BT. Local recurrence rates were 6% and 8.5%, respectively. Excellent or good cosmetic results were achieved in 83% and 88%, respe-ctively [7]. The differences between rates in the two gro-ups were not statistically significant.

Kulik from the Oncology Centre in Warsaw presented the results of a HDR BT boost study in 93 patients undergoing conservative treatment. During the 3-year follow-up one case of local recurrence was obs-erved; excellent or good cosmetic results were achieved in 85% of patients. In a ProbRough rule induction anal-

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ysis including all clinical and therapeutic variables it was shwn that patients with a mammography diameter of tumour not exceeding 11mm have the best chance of excellent or good cosmetic results [8].

We undertook this study, the second such study in our Department, to evaluate the effect of HDR BT boost versus electron beam boost on local tumor control, side effects and cosmesis after breast conserving surgery in early breast cancer

II. Methods

40 patients with invasive early-stage breast cancer (Stage I–II as defined by the AJCC 7th edition guidelines) were treated prospectively with breast conservation surgery. All patients signed informed consent forms prior to treatment. All the patients underwent tumorectomy ie. macroscopic total resection of the primary tumor. Re-excision to achieve negative surgical margins was performed as needed to obtain margins of 2 mm, if initially the surgical margin was positive. All patients underwent full axillary lymph node dissection (all III levels of the axillary fossa). The median number of lymph nodes excised was 16.

In all patients, adjuvant EBRT to the whole breast was used. Patients were positioned supinely on a breast board with both arms raised overhead. 3D CT planning of the breast was used. Patients were treated with two tangential fields with either gamma-rays from a cobalt unit or with 4-6 MV photon X-rays. Whole breast radiotherapy was delivered as 50 Gy in 25 fractions over 5 week.

Boost to the tumor bed was given to an equivalent dose of 15-16 Gy with either HDR BT using Iridiuim-192 interstitial temporary implants or electron beam using a linear accelerator. Electron beam boost was given in continuation with EBRT to maintain the continuity. There was one week gap between completion of EBRT and HDR BT boost to reduce chances of infection. In the HDR BT boost group, implants were designed to irradiate the lumpectomy cavity with at least a 1–2 cm margin. The dose rate was 350 cGy twice a day for two days. In the electron group the boost was 250 cGy once daily with 9-12 MeV electron over 6 days.

The toxicities and cosmesis were assessed at a specific time point: at 1.5 years of follow-up. The toxicity parameters examined included the following: breast edema, erythema, fibrosis, hyperpigmentation, hypopigme-ntation, breast pain, breast infection, telangiectasia, and fat necrosis. Toxicities were graded by using the Radiation Therapy Oncology Group (RTOG) / European Organization for Research & Training of Cancer (EO-RTC) late radiation morbidity scoring scheme and Com-mon Terminology Criteria for Adverse Events (CTC-AE) for skin, subcutaneous tissues, pain and derm-atitis. B-reast edema, erythema, pigmentary changes, and telan giectasia fell under the domain of radiation dermatitis and skin; breast fibrosis and breast pain were under the domains of subcutaneous tissues and pain due to radiation, respectively. Breast infections and fat necrosis were either present or not and were noted accordingly.

In accordance with the guidelines of Common Toxicity Criteria, version 4.0, toxicities were graded by using the acute/chronic radiation morbidity scale: Grade 0 - no observable radiation effects;
Grade 1 : mild radiation effects;
Grade 2 : moderate radiation effects;
Grade 3 : severe radiation effects.

Cosmetic evaluation was based on the standards set forth by the Harvard criteria as shown below in Table 1. The treating physician at a scheduled follow-up visit scored the cosmetic result. No patient-reported scoring of cosmetic outcome was done. Likewise, the treating radiation oncologist did all toxicity scoring for each patient.

Table 1

Harvard/NSABP/RTOG Breast Cosmesis Grading Scale

1. Excellent	When compared to the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast, but not enough to change the appearance.
2. Good	There is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3. Fair	Obvious difference in the size and shape of the treated breast. This change involves one-quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4. Poor	Marked change in the appearance of the treated breast involving more than one-quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

NSABP = National Surgical Adjuvant Breast and Bowel Project; RTOG = Radiation Therapy Oncology Group.

The statistical method employed for the incidence/severity of toxicities and cosmetic outcome with various parameters was Pearson chi-square analysis stratified for no toxicity versus any toxicity.

III. Results and Discussion

a) Review of Literature

Oedema of the breast, hyperpigmentation, hypopigmentation/ depigmentation of the nipple and papillae, teleangiectases and fibrosis are all cons-equences of radiation therapy [10]. Generally breast pain, edema, erythema, and hyperpigmentation all dim-inish in frequency over time. Edema of the breast is observed mainly during and directly the end of radiot-herapy. In 10-20% of patients, it can appear as a late reaction after 18-36 months after radiotherapy; in such cases it is moderate and reversible [10].

Sequelae that increases until the 2-year mark and later stabilizes includes breast fibrosis and hypopigmentation. Fat necrosis and telangiectasia increase with the passage of time. A study from Peter Y. Chen et al showed fat necrosis increased from 1% at 6 months to 9% at 2 years and 11% at 5 years. The median time to occurrence of fat necrosis was 5.5 years after completion of radiation therapy and HDR BT.

Telangiectases are observed mainly in areas of high doses of radiotherapy given by electrons or HDR BT or in areas of skin folds. They can be observed in 30% of patients and time to their appearance is the longest out of all side effects of radiotherapy. Contrary to other side effects, the probability and intensity of telangiectases increases in the course of follow-up. The most important late effect of radiation is breast fibrosis. Contrary to other factors, which are reversible (oedema) or limited to a small area of the breast (telangiectases), fibrosis encompasses the whole breast and is the most important factor of breast's retraction [10]. Fibrosis appears after 6-18 months and the highest intensity is observed after 3 years. Longer observations of patients did not reveal progression of the retraction of the treated breast. It is advised to perform cosmetic evaluation 3 years after primary treatment because at this point most late effects already appear. Late effects, those that appear years after, don't affect final cosmesis.

In our study we evaluated the cosmetic outcomes and adverse events at 1.5 years after the completion of whole breast EBRT and boost. So we did not evaluate the changing trends for these events and as such our study follow up was short.

Table 2 : Adverse events

	HDR BT Boost (% of patients)			Electron Beam Boost (% of patients)			p-value
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	
Breast Pain	15	5	0	15	0	0	0.211
Breast edema	15	0	0	10	0	0	0.161
Erythema	15	0	0	15	0	0	1.000
Hyperpig menatation	40	5	0	30	0	0	0.002
Hypopig Mentation	35	0	0	20	0	0	0.001
Fibrosis	50	5	5	30	0	0	<0.001
Telangiect Asia	25	5	0	20			0.029
Fat necrosis	10			5			0.095
Breast Infection	5			0			0.021

**Fat necrosis and infection are not graded.*

For the implant group, nearly all pigmentary changes, whether hyperpigmentation or hypopig-ment-ation, were pinpoint rather than diffuse, corresp-onding to the sites where the HDR catheters were been placed. Excellent or good cosmetic results were achi-eved in 10-0% and 90% patients of electron boost and HDR BT Boost respectively (p=0.0009), as shown below in table 3.

Table 3 : Cosmetic outcomes

	HDR BT Boost (% of patients)	Electron Beam Boost (% of patients)
Excellent	25	60
Good	65	40
Fair	10	0
Poor	0	0

In assessing toxicities and cosmesis, interpretations of changes like fibrosis and cosmetic outcomes are not entirely objective. In our study, grading of fibrosis was based on the degree of induration palpated at the time of each follow-up visit. Because induration dimesions were not always recorded, the grading by the examining clinician became the basis on which the degree of fibrosis was assessed. Fibrotic changes can be difficult to differentiate between sequelae from postsurgical changes and sequelae from radiation effects. Reexcision, such second surgical procedure, also contributed to breast fibrosis/induration. Thus, fibrosis is a conti-nuum and a morbidity of both surgical excision and a late radiation effect. It would be difficult to determine the proportional contribution of surgery versus the contribution of radiation that leads to fibrosis. However, we conservatively assigned any degree of induration under subcutaneous tissue-late RT morbidity scoring (fibrosis) solely related to a late radiation sequelae.

There was no significant difference in local tumor control between patients treated with electron bosst or HDR BT boost over a period of one and a half year in our study. The rate of local recurrence was same between the 2 patient groups: The HDR BT group demonstrated a local recurrence rate of 5% compared with patients who received electron beam boost, who had a similar 5% risk of local failure (p=1.00).

IV. Conclusions

Breast conservation therapy nowadays is an effective treatment for early breast cancer with more and more patients preferring this option due to better psychosexual quality of life. Breast conserving therapy in patients with early breast cancer allows us to achieve an excellent and good (satisfactory) cosmetic effect in a majority of cases (95% in our study). The results of the quailtative cosmetic evaluation vary between the patients and the physicians. We have done two such

studies to address cosmesis in BCT in our Department. In one of our studies, patients with early breast cancer after undergoing breast conserving surgery and whole breast irradiation have better cosmetic results and reduced chances of fibrosis at one and a half years of follow-up, when they are given electron boost as compared to HDR BT boost. Local tumor control rates were similar between the two groups. For local tumor control assessment long term follow up studies are needed.

Reaching an unequivocal opinion on which of the two boost techniques, TRT boost with electrons or HDR BT, is more efficient is not an easy task. Hammer et al. showed significantly lower local recurrence rates with significantly higher rate of excellent and good cosmetic results for the HDR BT, while the group from the National Oncology Institute in Budapest did not confirm these results in the settings of a randomized study [6,7].

It has been stated that publications showing inferior cosmetic outcomes after brachytherapy boost have lacked the necessary attention to technical details such as dose homogeneity. But this was not seen in our study. Recent experiences have demonstrated equivalent or superior results for HDR BT as compared to electron-beam boosting—despite the higher doses. Irrespective of the dose rate (HDR or LDR) better cosmetic results by BT boost can be explained by the lower dose delivered to the skin. This results from the fact that the distance between the most "superficial" interstitial guide needle and the skin should reach 5mm. Thus the danger of teleangiectasias and fibrosis, which significantly influences cosmetic outcomes, is reduced. Due to the beam geometry this cannot be achieved using electron beam TRT [9]. So the debate as to which is the optimal boosting technique goes on.

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